

Mechanism of toxicity of paraquat

Paraquat is readily reduced by microsomal enzymes from lung to a radical ion.⁸⁻¹⁰ In the presence of oxygen the radical ion is oxidized with the formation of superoxide which may damage cells directly or through the generation of other active oxygen species. The involvement of the redox cycling of paraquat in

its mechanism of toxicity is not in doubt. However the biochemical events leading to cell death have not been identified.⁶ Inhibition of the reduction of paraquat *in vivo* has not been achieved and in the absence of information on the subsequent biochemical events treatments based on inhibition or reversing these processes have not been developed.

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Paraquat poisoning: clinical features and immediate general management

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1 In contrast to 10-15 years ago most cases of paraquat poisoning are now due to deliberate self-poisoning with parasuicidal or suicidal intent rather than to accidental ingestion. Less commonly, poisoning may follow careless handling of paraquat during occupational use. Although paraquat can be absorbed through the skin if improperly handled, poisoning usually follows ingestion and has rarely been reported after subcutaneous, intravenous or intraperitoneal injection.

2 Clinically, three degrees of intoxication may be distinguished. (a) Mild poisoning occurs after the ingestion or injection of less than 20 mg of paraquat ion/kg body weight. In these cases patients are either asymptomatic or symptoms are confined to the gastrointestinal system. All patients recover fully. (b) Moderate to severe poisoning usually follows the ingestion (rarely injection) of 20-40 mg of paraquat ion/kg body weight. Non-specific symptoms of ill health together with local gastrointestinal symptoms precede the development of renal failure (which may recover spontaneously) and pulmonary fibrosis which may not be manifest for days or weeks. Death occurs in the majority of cases but is usually delayed for 2-3 weeks. (c) Acute fulminant poisoning follows the ingestion of substantial quantities of paraquat (> 40 mg of paraquat ion/kg body weight). In addition to local symptoms, multiple organ (cardiac, respiratory, hepatic, renal, adrenal, pancreatic, neurological) failure occurs. Death may supervene within hours and is never delayed for more than a few days.

3 Initial general management has four priorities. Firstly, fluid loss should be replaced; secondly, the prognosis should be determined by measurement of the plasma paraquat concentration; thirdly, symptoms due to ulceration of the oropharynx must be relieved; fourthly, supportive care for patients and relatives must be provided.

4 Experience suggests that management of the terminally ill patient with acute fulminant poisoning is a far greater clinical challenge to medical and nursing expertise than simply the employment of methods to prevent absorption or increase elimination of paraquat.

Introduction

Paraquat is a widely used herbicide that is marketed either in granular form (25-80 g/kg, e.g. Weedol, Pathclear, Speedway) or as a water-soluble concentrate (100-200 g/l, e.g. Gramoxone, Dextrone). In the UK, the concentrated preparations can, under poisons law [Poisons Act, 1972; The Poisons Rules 1982, The Poisons List Order, 1982 (as amended)], only be supplied to bona fide agriculturalists and horticulturalists.

Local toxicity: skin, nails, eyes, nose

Paraquat, especially in concentrated formulations, has a strong irritant action on various types of epithelia. Thus, it will cause erythema, blistering, irritation and ulceration of the skin and eczematous dermatitis has

been reported (Botella *et al.*, 1985). Paraquat diluted as recommended for spraying is unlikely to irritate the skin unless clothing soaked with spray is worn for prolonged periods.

Concentrated solutions of paraquat may also cause localized discolouration or a transverse band of white discolouration affecting the nail plate, though the latter damage may not become apparent for several weeks. Transverse ridging and furrowing of the nail progressing to gross irregular deformity of the nail plate and loss of nail may also occur (Samman & Johnston, 1969; Hearn & Keir, 1971; Botella *et al.*, 1985). Normal nail growth follows without delay once exposure has ceased.

Severe inflammation of the cornea and conjunctiva may follow the accidental splashing of paraquat concentrate into the eyes. The inflammation develops gradually, reaching a maximum after 12-24 h, and

may lead to ulceration of the conjunctiva and cornea (Joyce, 1969) with the risk of secondary infection. Although healing may be slow, recovery is usually, though not always, complete (Cant & Lewis, 1968a,b; Deveckova *et al.*, 1980). Serious ophthalmic complications may ensue if the casualty does not recognize the potential seriousness of exposure. In these circumstances, the patient may present with marked reduction in visual acuity due either to corneal oedema or a corneal opacity (Swan, 1968; Joyce, 1969). Lachrymal duct stenosis has also been described (Karai *et al.*, 1981).

Inhalation of fine spray droplets through careless use can cause epistaxis and sore throat.

Systemic toxicity

In contrast to 10–15 years ago, most cases of paraquat poisoning are now due to deliberate self-poisoning with parasuicidal or suicidal intent rather than to accidental ingestion, as may occur if the herbicide is decanted into a wine or soft-drink bottle. Occasionally, food and drink may be adulterated with paraquat with intent to harm (Watts, 1985) or murder (Teare & Brown, 1976). Less commonly, poisoning may follow careless handling of paraquat during occupational use. Although paraquat can be absorbed through the skin if improperly handled, poisoning more usually follows ingestion or, rarely, injection of the herbicide. There is no conclusive evidence that systemic toxicity has ever followed inhalational exposure to paraquat.

Systemic toxicity after percutaneous absorption

Normally, the surface epithelium of the skin is an excellent barrier to paraquat (Walker *et al.*, 1983), but prolonged skin contact with the herbicide may not only cause a chemical burn with blistering and ulceration but also serious and even fatal poisoning. Systemic toxicity is more likely to result if the paraquat solution is concentrated, exposure is prolonged and the skin traumatized (Newhouse *et al.*, 1978). These conditions may be encountered as the result of the following. (1) Poor occupational practice. The use of leaking spray apparatus (Jaros, 1978; Levin *et al.*, 1979; Withers *et al.*, 1979; Wohlfart, 1982; Athanaselis *et al.*, 1983), the non-use of protective clothing (Newhouse *et al.*, 1978), prolonged wearing of contaminated clothing and failure to wash contaminated skin (Athanaselis *et al.*, 1983), may all result in serious poisoning. (2) Carelessness. A farmer from Belize fell off his bicycle with a bottle of paraquat in his pocket. He did not remove his trousers for several hours and ultimately died 12 days later (Waight, 1979). In another incident, an adult cleaned his perineum with paraquat by mistake. He developed renal and respiratory failure and required mechanical

ventilation for 5 days but eventually recovered (Tungsanga *et al.*, 1983). (3) A mistaken belief in the therapeutic efficacy of paraquat. Paraquat has occasionally and inappropriately been used as a treatment for lice and scabies (Ongom, 1974; Binns, 1978; Wohlfart, 1982), sometimes with serious consequences. (4) Accident. After spillage of paraquat, children may be contaminated, their skin not washed, the danger to their health not recognized and severe complications ensue (Okonek *et al.*, 1983).

Systemic toxicity after injection

Systemic toxicity has followed the subcutaneous (Almog & Tal, 1967), intraperitoneal and intravenous (Harley *et al.*, 1977; Hendy *et al.*, 1984) injection of paraquat.

Clinical features of paraquat poisoning

This review is based on the personal clinical experience of the authors obtained through the treatment of approximately 150 patients. In addition, a comprehensive review of the literature has been undertaken, but, for the purpose of brevity, only references to uncommon complications have been cited. Three degrees of intoxication may usefully be distinguished.

Group 1

Mild poisoning follows the ingestion or injection of < 20 mg of paraquat ion/kg body weight [i.e. < 1 sachet of 2.5% (w/v) Weedol]. Patients are asymptomatic or develop vomiting and diarrhoea. Full recovery occurs but there may be a transient fall in the gas transfer factor (TLCO) and vital capacity.

Group 2

Moderate to severe poisoning follows the ingestion or injection of 20–40 mg of paraquat ion/kg body weight (i.e. > 1 sachet of 2.5% (w/v) Weedol or < 15 ml of 20% (w/v) concentrate]. Patients suffer vomiting and diarrhoea and develop generalized symptoms indicative of systemic toxicity. Pulmonary fibrosis develops in all cases but recovery may occur. In addition, renal failure and, sometimes, hepatic dysfunction may supervene. Death occurs in the majority of cases but can be delayed for 2 or 3 weeks.

Group 3

Acute fulminant poisoning follows the ingestion of more than (usually considerably in excess of) 40 mg of paraquat ion/kg body weight [i.e. > 15 ml of 20% (w/v) concentrate]. In addition to nausea and vomiting, there is marked ulceration of the oropharynx with multiple organ (cardiac, respiratory, hepatic, renal, adrenal, pancreatic, neurological) failure. In this group, at least in our experience, the mortality is

100%. Death may occur within 24 h of the overdose but is never delayed for more than 1 week.

Oropharyngeal and gastrointestinal symptoms

Paraquat itself causes nausea, vomiting (rarely blood stained) and diarrhoea as a result of its local irritant action on the gut. PP796, a phosphodiesterase inhibitor added as an emetic to nearly all recent paraquat formulations, stimulates directly the vomiting centre after absorption. Granular preparations contain magnesium sulphate which increases the likelihood of diarrhoea. The corrosive action of paraquat causes patients who are moderately or severely poisoned to develop a burning sensation, soreness and pain in the mouth, throat, chest (retrosternally) and abdomen (usually epigastric and is sometimes associated with guarding). Ulceration in the mouth, sloughing of the oropharyngeal mucosa, an inability to swallow saliva ('pseudo-hypersalivation'), dysphagia and aphonia are common. Prominent pharyngeal membranes ('pseudodiphtheria') have been reported (Stephens *et al.*, 1981) and perforation of the oesophagus may result in mediastinitis, surgical emphysema (Figure 1) and pneumothorax.

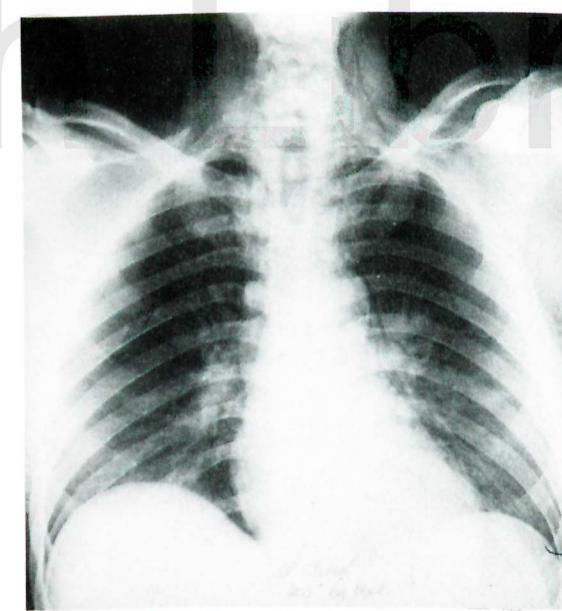


Figure 1 Chest X-ray in a patient who developed perforation of the oesophagus, mediastinitis and surgical emphysema

General symptoms

Within 24 h of ingestion patients in groups 2 and 3 develop lethargy, a widespread burning sensation, generalized weakness and myalgia, giddiness, headache, anorexia and fever. Fear and apprehension are

prominent features and restlessness is sometimes observed.

Renal, hepatic and pancreatic symptoms

Oliguric or non-oliguric renal failure may supervene and is due usually to acute tubular necrosis though, exceptionally, glomerular and tubular haemorrhage may be found (Kodagoda *et al.*, 1973). Proximal tubular dysfunction which results in proteinuria, microscopic haematuria, glycosuria, aminoaciduria, phosphaturia and excessive leaking of sodium and urate is common (Vaziri *et al.*, 1979).

Jaundice, hepatomegaly and central abdominal pain due to pancreatitis, together with associated biochemical abnormalities are frequent complications in patients severely poisoned with paraquat. Centrilobular hepatic necrosis and cholestasis are seen at post mortem examination in these patients.

Respiratory features

Most patients develop a cough which may be productive and blood stained. Dyspnoea is a prominent feature and occurs early in those patients who have ingested a substantial amount and, in these circumstances, is due to the development of the adult respiratory distress syndrome. In less severely poisoned patients the onset of dyspnoea may be delayed and is then caused by pulmonary fibrosis. Rarely, pneumothorax (in association with mediastinitis), pleural effusion and iatrogenic pulmonary oedema, may precipitate dyspnoea.

In addition to a falling gas transfer factor (TLCO) and vital capacity (which may return to normal in patients in group 1 and, less commonly, in those in group 2), severely poisoned patients will have a low and falling P_{O_2} with resultant central cyanosis. Radiological changes do not always parallel the severity of clinical symptoms. Thus, the chest X-ray may be normal particularly in those dying early from multiple organ failure. More usually, patchy infiltration occurs (Figure 2) which may progress to an opacification of one (Figure 3) or both (Figure 4) lung fields.

Cardiovascular features

Except for sinus tachycardia, cardiovascular complications are not usually observed until the terminal phase of intoxication. Then, ventricular tachycardia, intraventricular conduction disturbances, and non-specific T-wave changes on electrocardiogram occur. Sinus bradycardia, hypotension and cardiac arrest may supervene. The chest X-ray may show massive cardiomegaly and, at post mortem, toxic myocarditis is found histologically.

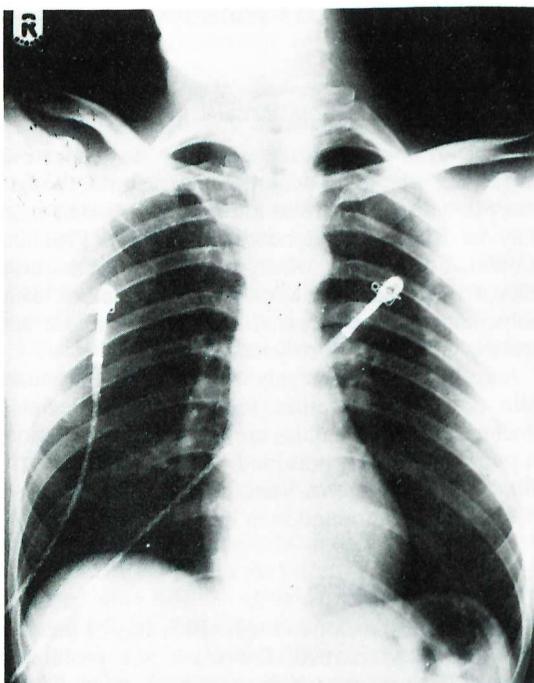


Figure 2 Chest X-ray on admission (a) and 15 days later (b) showing patchy infiltration in both lung fields

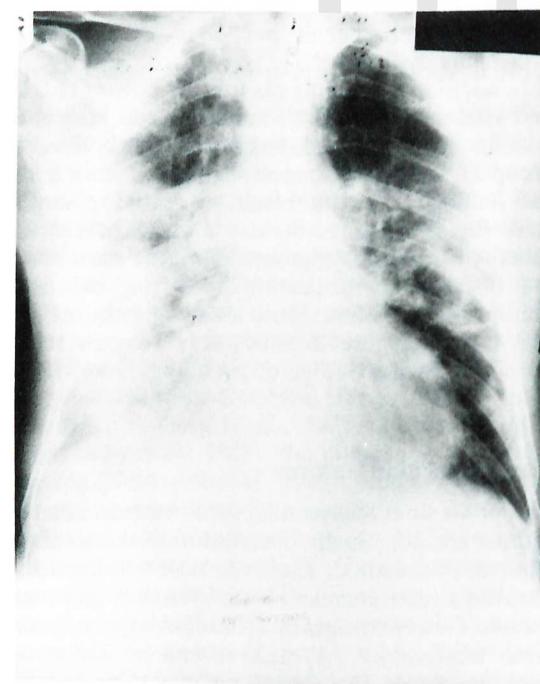


Figure 3 Chest X-ray showing patchy infiltration in both lung fields with partial opacification of the right

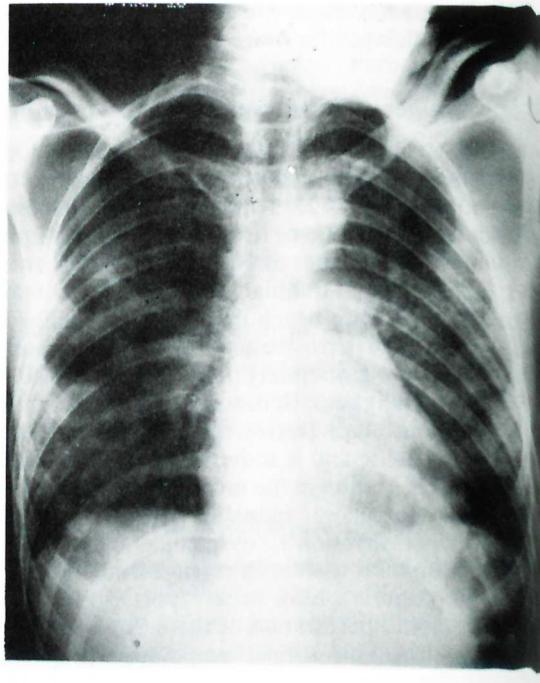
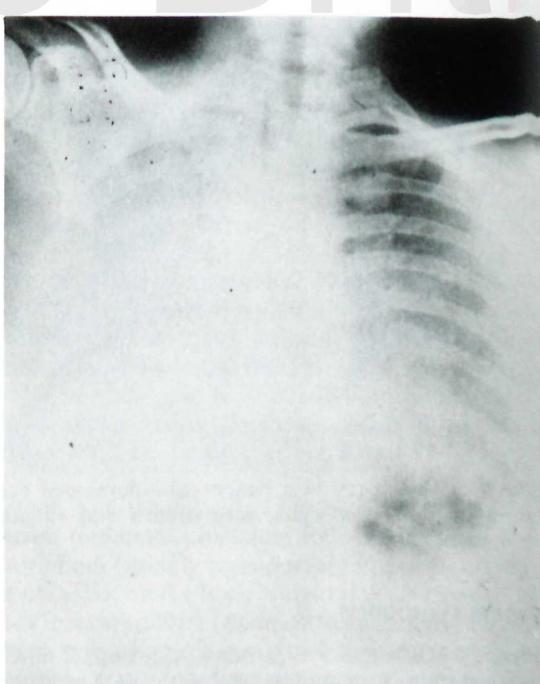


Figure 4 Chest X-ray showing total opacification of the right lung field and partial opacification of the left field



Neurological features

Coma is a common and terminal event, though other neurological features such as ataxia and facial paresis (Almog & Tal, 1967) are occasionally observed. Convulsions have been reported (Mickelson & Fulton, 1971; Conradi *et al.*, 1983; Addo *et al.*, 1984) and may be due to cerebral oedema (Grant *et al.*, 1980) precipitated by fluid overload (Fennelly *et al.*, 1971).

Adrenal cortical necrosis

At post-mortem examination adrenal cortical necrosis is often observed (Nagi, 1970; Kodagoda *et al.*, 1973; Reif & Lewinsohn, 1983) particularly in severely poisoned patients with multiple organ failure (group 3). The clinical significance of this observation is unclear since the use of corticosteroids does not correct hypotension, which is more probably due to myocardial failure.

Haematological and biochemical abnormalities

A polymorphonuclear leucocytosis is a frequent finding but, rarely, erythrocyte aplasia, leading to a normochromic anaemia (Lautenschlager *et al.*, 1974) and haemolytic anaemia (Fairhurst *et al.*, 1976) have been reported. Metabolic acidosis, probably secondary to cardiovascular collapse and hypoxia, is a common complication. Hypocalcaemia, which sometimes results in tetany, is usually iatrogenic after either inappropriate attempts at forced diuresis in the presence of renal impairment (Fennelly *et al.*, 1971) or charcoal haemoperfusion (Sieken, 1982). In addition, elevation of serum creatinine kinase activity is seen, secondary to paraquat-induced muscle damage.

General management

Initial management has four priorities. Firstly, fluid loss should be replaced; secondly, the prognosis should be determined; thirdly, symptoms due to ulceration of the oropharynx must be relieved; fourthly, appropriate supportive care for patients and relatives must be provided. In addition, it may be appropriate to consider referral to a specialist treatment centre.

The value of methods to prevent absorption are discussed critically in a separate paper (Meredith & Vale, 1987).

Fluid replacement

There is good evidence that, as a result of vomiting and diarrhoea and the administration of purgatives, many patients poisoned with paraquat are fluid depleted (Williams *et al.*, 1984). An intravenous

infusion should therefore be commenced on admission to reduce the risk of renal dysfunction and diminished renal excretion of paraquat.

Assessment of prognosis

The history is a good general guide in that the ingestion or injection of the 20% (w/v) paraquat concentrate will invariably lead to severe poisoning. If a granular preparation has been ingested, a qualitative urine test should be performed with alkaline sodium dithionite (Braithwaite, 1987). If this test is negative within 24 h of the overdose there is no clinical need for a quantitative assay on the blood and the patient may be reassured accordingly. If, however, the urine test is positive, measurement of the plasma paraquat concentration is extremely helpful and may be interpreted by reference to published data (Proudfoot *et al.*, 1979; Hart *et al.*, 1984; Scherrmann *et al.*, 1987).

Referral to a specialist centre?

If the diagnosis of paraquat poisoning is confirmed, the decision as to whether to refer the patient to a specialist poisons treatment centre should be taken. At least in the UK, the majority of doctors and nurses at local hospitals have not managed personally a case of severe paraquat poisoning and this lack of clinical experience, combined with the knowledge that the mortality is high, engenders a feeling of uncertainty in the staff concerned which is often then recognized by patients and relatives. In contrast, a specialist centre will have considerable medical and nursing expertise available not only to relieve the local and systemic effects of paraquat poisoning but also to employ elimination techniques if appropriate (Proudfoot *et al.*, 1987).

Referral to a treatment centre may make visiting for the relatives difficult and arrangements must be made for relatives to stay in the hospital if they so wish. Our experience suggests that relatives are comforted by the fact that 'everything has been done' to make the patient's final days as comfortable as possible and this overrides any geographical inconvenience. At the same time it must be recognized that nursing staff in a specialist unit may themselves be distressed by the high mortality among patients poisoned with paraquat. In addition nurses who see themselves as intensive- or critical-care specialists may not welcome the need to practice terminal care.

Terminal care: relief of local pain and general distress

It is of vital importance that the patient is not neglected or isolated. Frequent visits from medical and nursing

staff are mandatory as bad or infrequent communication causes considerable suffering to the patient. Those who are dying reach out for support and companionship not only from their friends and relatives but from their medical advisers too. If asked, one should be honest about the prognosis, whilst at the same time offering hope. For 'the aim is to make dying a little easier, not to apply the dogma of always divulging the truth' (Hinton, 1967). It is reassuring to explain to the patient that 'we have managed patients like you before. No matter what happens we shall stand by you — we will not let you down'. This confident and supportive attitude reduces fear and despair. Above all, attention should be directed away from incurable organ damage to the alleviation of symptoms as there is always something that can be done to provide symptomatic relief.

Pain and distress should be reduced to a minimum. It is difficult to abolish the severe pain produced by local ulceration. Mouth washes, ice-cold fluids (e.g. ice-cream, lemon mucilage), local anaesthetic sprays and lozenges have all been employed with varying degrees of success. Opiates will be required eventually in most patients to relieve general, as well as local, pain and distress. Above all, inappropriate treatment

should be avoided. Thus, for example, the repeated use of cathartics when the outlook is hopeless is therapeutically irrelevant and clinically harmful. One needs to remember that 'the emotional isolation of the dying may be diminished if all who care for him are aware of the problem and treat the patient with kindness, understanding and as an intelligent adult capable of adjusting to the truth.' (Twycross, 1975).

Managing the relatives

Relatives want and need an authoritative prognosis which it is now possible to give. Yet hope should not be removed completely, because the relatives need help to adjust to the probable death of the patient. It is appropriate and worthwhile to encourage the relatives to talk about the patient and to assist them, if necessary, to heal or reinforce their relation with the patient. Occasionally, relatives must be reminded that the patient's trust cannot be compromised by deceit when they insist that the patient is not told the truth about his illness.

The authors offer their thanks to nursing colleagues who have helped them to manage patients and their relatives.

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